

REMARKS

FORMAL MATTERS:

Claims 48-56, 58-67, 69-72, 74-81 and 83-91 are currently pending.

Claims 48-56, 58-67, 69-72, 74-81 and 83-91 are rejected.

WITHDRAWN REJECTIONS

The Applicants thank the Examiner for indicating that the prior rejections under 35 U.S.C. § 112, paragraph 1 (enablement) and paragraph 2 (indefiniteness) have been withdrawn.

REJECTIONS UNDER §103(A)

Claims 48-56, 58-67, 69-72, 74-81 and 83-91 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Wappler et al. (33 Anesthesiol. Intensivmed. Notfallmed. Schmerzther. 18 (1998), references herein to page numbering of English translation) (“Wappler”) combined with Wagemans et al. (2 Oncologist 70 (1997)) (“Wagemans”), Peterson et al. (US Pat. 6,524,305) (“Peterson”) and Nelson et al. (US Pat. 5,980,927) (“Nelson”).

The Proposed Combination of References Fails to Teach or Suggest Each and Every Element of the Claims

In the communication filed on Nov. 30, 2009, the Applicants argued that the combination of Wappler, Wagemans, Peterson and Nelson fails to teach or suggest each and every claim element. The methods of independent claims 48 and 63 each require systemically administering a composition comprising sufentanil to a subject, wherein the sufentanil is present in the composition at a concentration of about 0.5 mg/ml to about 500 mg/ml. There is no teaching or suggestion of a concentration in that range within the combination of references. The Office rejects the above argument and responds by alleging that “Wappler teaches delivery of the same amount of sufentanil per day, and teaches the same delivery rate, and this suggests the same total concentration in device as instantly claimed.” Final Office Action, page 10. The Applicants respectfully disagree.

The portions of Wappler cited in the Office Action indicate that sufentanil was provided intravenously in a dose between 0.075 to 2.5 µg/kg/hr. According to the Office, for the average person

weighing 60 kg, this equates to a disclosed range from 4.5 µg/hr to 150 µg/hr, which is 0.098 to 3.6 mg/day. The Office further calculates the delivered doses of claims 48 and 63 to be between 0.0025 mg/day to 1000 mg/day. The Office concludes that, because Wappler's disclosed mass per time dosage is allegedly encompassed by the mass per time dosage of the claims, it "suggests the same total concentration in device as instantly claimed." *Id.* However, there are countless theoretical combinations of concentration and volume per time that yield identical mass per time dosages. For instance, delivery of 100 µg/hr could be accomplished either by delivering 1 µl/hr of a 100 mg/ml solution or by delivering 100 µl/hr of a 1 mg/ml solution. This example illustrates that the mass per time delivery rate (in this example, 100 µg/hr) is not suggestive of the concentration of the solution delivered (in this example, either 1 or 100 mg/ml). Likewise, Wappler provides absolutely no teaching or suggestion based on the alleged mass per time dosage as to the concentration of sufentanil in the composition.

Moreover, because Wappler delivers sufentanil intravenously whereas the instant claims deliver sufentanil via an implantable convective delivery system, it is likely that Wappler uses concentrations considerably lower than that of the instant claims. Note that each of claims 48, 63, and 84 indicate that sufentanil is delivered from the device at a low volume rate of from about 0.01 µl/day to about 2 ml/day. Wappler is silent as to the volumetric rate of delivery, but intravenous infusions of analgesics are commonly given at a volume rate of 2ml/kg/hr, or 2880 ml/day for an average person weighing 60 kg.¹ Even long-term (e.g., 12-hour) intravenous infusions are commonly given at a volume rate of 0.5 ml/min, or 720 ml/day.² Accordingly, since Wappler likely delivered a much larger volume than the claims call for, Wappler also likely delivered sufentanil in a far lower concentration than the claims indicate. Even if Wappler delivered only 200 ml/day, a much lower volume per day than other intravenous methods,³ Wappler would disclose at most a sufentanil concentration of .018 mg/ml (i.e.,

¹ See, e.g., Ogawa et al., *Intravenous Sedation with Low-Dose Dexmedetomidine: Its Potential for Use in Dentistry*, 55 Anesth. Prog. 82, 83 (2008). Note that this rate does not depend on the drug used because it is a volumetric rather than a weight-based rate of delivery.

² See, e.g., Nishikimi et al., *Effects of Long-Term Intravenous Administration of Adrenomedullin (AM) Plus hANP Therapy in Acute Decompensated Heart Failure—A Pilot Study*, 73 Circ. J. 892, 893 (2009).

³ Note that Applicants do not acknowledge that Wappler used such a low volume. This number is chosen only to emphasize that Wappler would have had to deviate quite substantially from standard protocols in order to approach concentrations as high as those presently claimed.

the maximum calculated dose of 3.6 mg/day divided by the minimum volume rate of 200 ml/day). This concentration is more than 20-fold below the low end of the instantly claimed range of about 0.5 mg/ml to about 500 mg/ml. Thus, Wappler fails to teach or suggest a sufentanil concentration of about 0.5 mg/ml to about 500 mg/ml or a low volume rate of delivery from about 0.01 µl/day to about 2 ml/day.

Not one of Wagemans, Peterson or Nelson teach or suggest the specifically claimed sufentanil concentrations. Accordingly, the inclusion of these references in the proposed combination does nothing to cure the identified deficiencies in Wappler. On this basis, Applicants respectfully request reconsideration and withdrawal of the rejection.

Wagemans Teaches Away from the Claimed Invention

“A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, **or would be led in a direction divergent from the path that was taken by the applicant.**” *In re Gurley*, 27 F.3d 55, 553 (Fed. Cir. 1994)), (emphasis added). Wagemans teaches the advantages of local spinal administration of opioids and compares these advantages with the disadvantages associated with systemic administration of opioids. Accordingly, Wagemans directs one of ordinary skill in the art away from a method as presently claimed which requires systemically administering sufentanil.

Wagemans clearly characterizes epidural and intrathecal administration as two types of spinal administration. Furthermore, Wagemans characterizes spinal administration as local administration in the context of opioid treatment, i.e., Wagemans indicates that the drug is administered directly to the receptor site location. See, e.g., Wagemans at page 71, left column. Finally, Wagemans provides several advantages of spinal, i.e., local administration relative to systemic administration, but fails to discuss advantages of systemic administration relative to local administration. Specifically, the reference discusses:

- “the ability [of local administration] to reach higher concentrations of opioids at the receptor site when compared with systemic administration” (Wagemans, page 71, left column),

- “[t]he normal dosage of spinal opioids [for local administration] is considerably lower than systemic opioid dosage, therefore producing fewer side effects” *Id.*, and
- “[c]onstipation is not commonly seen after spinal administration of opioids, but frequently occurs after systemic administration” *Id.*

Applicants submit that when the reference is examined for its comparison of local administration to methods of systemic administration, there is a clear teaching away from systemic administration in favor of local administration. Accordingly, Wagemans is not properly combinable with the remaining references in the manner suggested by the Office.

No Apparent Reason to Combine Wappler with Wagemans in Combination with Peterson and Nelson

Applicants respectfully submit that there would have been no apparent reason for one of ordinary skill in the art to combine the disclosed delivery rates of Wappler in the proposed combination which utilizes the continuous infusion method described by Wagemans. This is because the method of Wagemans which involves the local administration of opioids directly to the spinal cord differs completely from Wappler’s intravenous, systemic administration method.

The Office rejects this argument and responds by alleging that:

- 1) “[t]he claims do not require any specific site of administration” (Final Office Action, page 12),
- 2) Wagemans “teaches systemic absorption of opioids delivered by epidural and intrathecal routes,” (Final Office Action, page 12) and
- 3) “even with local administration, it is inevitable to have some opioid absorbed systemically from the local administration site to provide systemic effect.” Final Office Action, page 13.

The Applicants respectfully disagree with these assertions and their applicability to the present argument. As an initial matter, Applicants note that the Office’s argument that the claims “do not require any specific site of administration” (Final Office Action, page 12) does nothing to refute Applicants’

argument that there would have been no apparent reason for one of ordinary skill in the art to have combined the teachings of Wappler and Wagemans with the teachings of Peterson and Nelson in the manner suggested by the Office. In addition, Applicants respectfully submit that the Office's characterization of the claims is inaccurate. By their plain language the claims require more than a systemic effect. The claims specifically require “**systemically administering**” a composition comprising sufentanil to the subject. Accordingly, Wagemans solves the problem of providing analgesia in a subject in a completely different manner (i.e., **local administration**) than that employed by Wappler or that described in the instant claims.

Wagemans teaches spinal administration of opioids, which has the advantageous “ability to reach higher concentrations of opioids at the receptor site when compared with systemic administration.” Wagemans, page 71, left column, second paragraph. It is in this context that the language cited by the Office Action must be read.⁴ Accordingly, Wagemans' alleged disclosure of systemic absorption during epidural or intrathecal administration is properly seen as recognition of a negative effect, not a “teaching” that one of skill in the art would view as desirable. See, e.g., Wagemans, page 72, right side, top paragraph, discussing “[t]he risk of systemic opioid side effects” If anything, this disclosure by Wagemans would lead one of skill in the art away from systemic administration as suggested in Wappler.

The Office' asserts that Wagemans' disclosed methods inherently result in some systemic absorption. However, even if true, this does nothing to refute the Applicants' assertion that there is no reason to combine Wappler and Wagemans. Even if Wagemans' methods unintentionally result in some systemic absorption, it remains true that Wappler's intravenous, systemic administration is of a wholly different type than Wagemans' local, spinal administration. As noted above, one of skill in the art would read Wagemans as teaching the disadvantages of systemic administration. If one of ordinary skill in the art were attempting to modify Wagemans, he/or she would not look for assistance in Wappler's systemic administration method because it would defeat Wagemans' strategy of avoiding systemic administration.

⁴ MPEP § 2141.02 (VI) A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. Citing *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540 (Fed. Cir. 1983).

In view of the above, Applicants submit that one of ordinary skill in the art would have had no apparent reason to combine Wagemans, Wappler, Peterson and Nelson in the manner suggested by the Office.

Nelson Teaches Away from the Combination with Wappler, Wagemans and Peterson and Teaches Away from the Claimed Invention

Nelson teaches away from the proposed combination of references which includes Wappler among others and further teaches away from the claimed invention. Rather than administering a drug systemically as suggested in Wappler, Nelson provides a device and method for administering an analgesic directly to the neuraxis of an organism.

In response, the Office argues that Nelson teaches treatment of chronic pain, and does not limit the site of pain. Applicants respectfully disagree. “A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention.” MPEP § 2141.02 (VI). When viewed as a whole, it is clear that the teaching of Nelson would lead away from a method of systemic administration. Specifically, Nelson states that “[t]he current regimen for treatment of these patients is systemic administration of relatively high doses of analgesics by for example oral, subcutaneous, intramuscular, intravenous and related routes on a daily or continuous basis.” Nelson goes on to describe problems associated with various methods of systemic administration of opioid analgesics. See, for example, Nelson at column 1, lines 28-49. Finally, Nelson indicates that “[t]he present invention provides an alternative means for achieving continuous central nervous system administration of an analgesic into the neuraxis via intraventricular, epidural, intrathecal and related routes for those suffering chronic pain and is directed to solving one or more of the problems noted above.”

By describing the various problems associated with systemic administration of opioid analgesics, and by offering its own device and method as an alternative, Nelson clearly teaches away from the systemic administration of opioid analgesics such as sufentanil. In direct contrast to Nelson, Wappler suggests systemic administration of drug as discussed above. Wappler points the ordinarily skilled artisan towards the systemic administration of opioids. Nelson states a goal of avoiding systemic administration, and provides a method to accomplish delivery directly to the central nervous system. As

such, one of ordinary skill in the art would be directed away from the combination with Wappler given Nelson's teaching that the systemic administration of these analgesics is undesirable.

Furthermore, the claims as currently amended specifically recite "**systemically administering**" a composition. As such, Nelson, which teaches away from the systemic administration of opioids, teaches away from the claimed invention. The Office cannot look to Nelson for an alleged teaching that a loading dose sufficient for long periods of administration can be calculated if the daily dose is known without also considering those portions of Nelson which teach away from the proposed combination and the claimed invention.

The Office argues further that Nelson's device does in fact provide systemic administration reciting that "even with local administration, it is inevitable to have some opioid absorbed systemically from the local administration site to provide systemic effect" (Final Office Action, page 14).

This argument appears to confuse obviousness with anticipation. An inherency argument is simply irrelevant to whether a reference teaches away from a claimed invention.⁵ The relevant question is not whether Nelson's device unintentionally allows some systemic absorption of opioid analgesics; rather, the relevant question is whether Nelson's explicit teaching that the device disclosed therein avoids the problems of systemic administration would dissuade one of skill in the art from combining Nelson with the other cited references to arrive at the claimed invention.

The Applicants renew their assertion that one of skill in the art, attempting to practice the claimed systemic administration method, would be discouraged from following the path set out in Nelson.⁶ Nelson's cataloging of the defects associated with systemic administration would suggest to

⁵ See, e.g., *Kloster Speedsteel AB v. Crucible, Inc.*, 793 F.2d 1565, 1576 (Fed. Cir. 1986) ("[Defendant's argument that inherency renders a property obvious] is unpersuasive when confronted by [defendant]'s failure to establish at trial that that inherency would have been obvious to those skilled in the art when the invention of claim 4 was made. Inherency and obviousness are distinct concepts.") (citing *W.L. Gore & Assocs. v. Garlock, Inc.*, 721 F.2d 1540, 1555 (Fed. Cir. 1983)), *overruled on other grounds by Knorr-Bremse Systeme Fuer Nutzfahrzeuge GmbH v. Dana Corp.*, 383 F.3d 1337 (Fed. Cir. 2004).

⁶ *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994).

one of skill in the art that Nelson's teaching is not helpful for those attempting to practice the claimed systemic administration method. Indeed, Nelson's device is to be implanted directly in the spinal column, the site of drug action, so as to minimize side effects associated with systemic administration.

Accordingly, Nelson teaches away from the claimed invention and thus may not be combined with the remaining references.⁷ The Applicants therefore respectfully request that the rejection be withdrawn.

⁷ See MPEP § 2145(X)(D)(2).

CONCLUSION

The Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number DURE-007CON2.

Respectfully submitted,
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Enclosure(s): Nishikimi et al. (2009)
Ogawa et al. (2008)

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